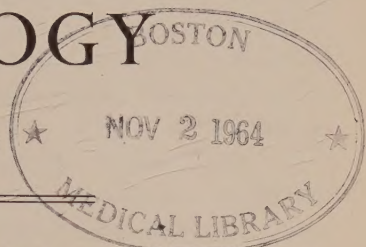


THE BRITISH JOURNAL OF DERMATOLOGY

OCTOBER 1956



THE PATHOLOGICAL VARIETIES OF VITILIGO AND THEIR RESPONSE TO TREATMENT WITH MELADININE.

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VITILIGO is a disorder of melanogenesis, and is characterized by depigmented areas occurring on otherwise normal skin. Any part of the body may be affected; the area involved is usually limited, but occasionally large patches cover most of the body. The ultimate cause is not known, but it is thought that there is inhibition of the tyrosinase activity of the melanocytes. These pigmentary dendritic cells, which are the only cells in the epidermis capable of producing melanin, are still present in vitiliginous lesions, but they are inactive (Becker, 1933 ; Becker *et al.*, 1952).

Little is known regarding the mechanism of the response of this disorder to various treatments. Recently a coumarin derivative, Meladinine, has been reported to be effective in restoring pigmentation when applied locally or taken by mouth (El Mofty, 1948 ; Sidi *et al.*, 1951 ; Lerner *et al.*, 1953 ; George *et al.*, 1955 ; Kanof, 1955). Previous investigators have confined their attention to either the biochemical or the clinical aspects of this treatment. No detailed histological studies of the disease and its response to treatment have been undertaken since Kissmeyer (1920) investigated the effects on vitiligo of ultra-violet rays from a Finsen lamp.

Theoretically, as a result of treatment, repigmentation might occur in one or more of the following ways :

(i) The melanocytes might regain tyrosinase activity.

(ii) Melanocytes might migrate into the affected area from the surrounding normal skin and replace the inefficient, DOPA-negative melanocytes (Kissmeyer, 1920).

(iii) Functioning melanocytes might migrate from underlying unaffected hair follicles (Pegum, 1955).

(iv) In some cases the vitiligo might not be complete, and some normal melanocytes might remain (Kissmeyer, 1920). Hyperfunction of these cells, or an increase in their number as a result of treatment, might result in repigmentation.

(v) The residual normal melanocytes at the periphery of a lesion, when stimulated by Meladine, might progressively transform the defective melanocytes within the lesion. Billingham and Medawar (1948) found that, in the skin of guinea-pigs, the more intensely pigmented black melanocytes could convert their neighbours into highly active melanocytes like themselves.

In order to determine which of these possibilities operated in the repigmentation of our successful cases, we employed the skin-splitting technique of Medawar (1941), and the DOPA staining method of Bloch (1917a) as modified by Becker (1927).

INVESTIGATION.

A series of cases of vitiligo were treated by the local application of Meladine and exposure to ultra-violet rays. Meladine is a mixture of two psoralens, 8-methoxypsoralen and 8-isoamyleneoxypsoralen. One ml. of solution as supplied by the Memphis Chemical Company contained 7.5 mg. of each of these psoralens. As this solution in its original strength sometimes caused acute reactions with blistering, we diluted this to 12.5% of its initial concentration with acetone. This $\frac{1}{8}$ -strength solution was used for the first few paintings, and if no untoward reactions occurred the strength was increased to 25% of the original. If this caused no erythema or blistering, the patients were then painted with half-strength or the undiluted solution. The affected areas of skin were painted two or three times a week. In some cases, if the response was slow, and there were no acute reactions, the patients were given some of the solution and told to paint themselves daily. In these circumstances, $\frac{1}{4}$ -strength solution was used in the summer months and full strength during the winter.

After painting, the affected skin was exposed to ultra-violet rays. In the first cases a mercury vapour source was used, either twice or three times weekly. This treatment proved unsatisfactory, and all later investigations were conducted with natural sunlight. This made the treatment of patients during the winter months impracticable.

Thirty-three biopsies were made from a total of 14 cases of vitiligo; four additional patients were treated, but biopsies were not performed as the

affected areas were on the face. Of the 18 patients, 14 were Europeans, two were West Africans, one was an Indian, and another one a Jamaican. Biopsy specimens were taken from the border region of the vitiligo patch, so as to include both normal and affected skin.

Histological technique.—The material was prepared by using the skin-splitting technique of Medawar (1941) modified by Szabó (1955). By this method the dermis was separated from the epidermis by the enzymic action of buffered commercial trypsin solution. Thus the basal layer of the epidermis, the site of the melanocytes, was freely exposed to observation. After a short fixation (2% formaldehyde-saline), the melanocytes were selectively stained with 1 : 1000 DOPA, buffered with phosphate to pH 7.4. The specimens were finally fixed in 4% formaldehyde-saline and counterstained with paracarmine.

In those specimens in which the DOPA did not stain the melanocytes, these DOPA-negative dendritic cells, or their derivatives the Langerhans cells (Masson, 1948; Billingham *et al.*, 1953), could be demonstrated with paracarmine or by supravital staining with methylene blue (Billingham, 1948; Becker *et al.*, 1952).

In all biopsies in which there were DOPA-positive melanocytes, these cells were counted and the results expressed per square millimetre ($\pm$ the standard error of the mean) of the skin surface in plane projection.

RESULTS.

Histological observations.—The normal architecture of the dermo-epidermal junction of the human skin and the distribution of melanocytes have already been described by Billingham (1948, 1949), Medawar (1953), and Szabó (1954).

There is a wide range of variation of the number of melanocytes, and of the epidermal pattern, in different regions of the body; also there are marked variations from one individual to another. Generally, there are 500–2000 melanocytes per sq. mm. of skin surface, except on the face, forehead, and behind the ears, where there are 1500–4000 per sq. mm. (Szabó, 1954).

To illustrate our findings with the pathological material, three cases will be considered in detail.

Case 1. A woman aged 40 years.

This patient had extensive lesions of 11 years' duration. Her arms, hands, thighs, and trunk were affected with multiple patches of vitiligo. She was treated with Meladinine and exposed to sunlight, and developed an acute erythema with blistering. After the reaction had subsided there was a slight perifollicular pigmentation in the treated area; otherwise there was no change as a result of treatment. Biopsies were taken before treatment from both affected and unaffected skin.

Histological findings.—The normal area from her thigh is shown in Fig. 1, and Fig. 2 is a neighbouring vitiliginous lesion. The structure of both areas is the same, but in the affected skin there is a total absence of DOPA-positive melanocytes. The distribution and number of melanocytes in the normal skin are within the usual

range for the human thigh (mean number per sq. mm. 960 ± 15). With paracarmin staining it was possible to detect dendritic cells in the vitiliginous area; these cells are DOPA-negative melanocytes. This type of lesion, in which there is a complete absence of DOPA-positive melanocytes, we have designated "Absolute".

Case 2. A man aged 74 years.

This man developed vitiligo of his hands and forearms five months before treatment. Biopsies were taken from normal and affected skin, before treatment with Meladinine and solar irradiation. He responded well, and after 5 weeks the painted lesions on his hands and forearms became repigmented. Further biopsies were taken from a repigmented lesion and from an untreated (control) vitiliginous area.



FIG. 1.—Case 1. Epidermal sheet of normal thigh skin, showing melanocytes on the epidermal ridges. The melanocytes over the dermal papillae are out of focus. $\times 290$. DOPA and paracarmin.

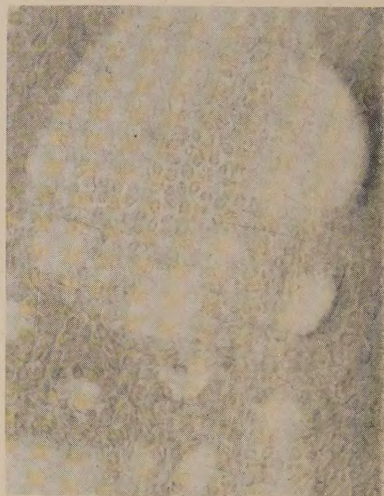


FIG. 2.—Case 1. Neighbouring vitiliginous area on thigh. Complete absence of DOPA-positive melanocytes. $\times 290$. DOPA and paracarmin.

Histological findings.—The normal skin of his forearm contains normal DOPA-positive melanocytes (Fig. 3) in numbers characteristic for this region (mean number per sq. mm. 1180 ± 40). In the affected area, however, the melanocytes are only very slightly DOPA-positive, and they are small and rounded (Fig. 4). Their dendritic processes are very short or invisible (mean number per sq. mm. 1290 ± 50). These weakly DOPA-positive cells and their derivatives, the Langerhans cells, were well shown in the epidermis stained with supra-vital methylene blue.

A treated area of vitiligo is shown in Fig. 5; the melanocytes have increased their tyrosinase activity and have become strongly DOPA-positive, but their number has not increased. This area became clinically repigmented.

A biopsy from a control, untreated, patch of vitiligo did not show any evidence of increased activity of the melanocytes.

This type of vitiligo, which histologically shows the presence of only slightly DOPA-positive melanocytes, we have named "Relative Type 1". The term "relative" is used because the skin is lacking in pigmentation only relatively to the

surrounding normal skin, and in this, of course, differs from those cases completely devoid of pigment. This patient improved as a result of treatment, a further distinction from the Absolute type.



FIG. 3.—Case 2. Normal epidermis. Numerous DOPA-positive melanocytes. $\times 290$. DOPA.

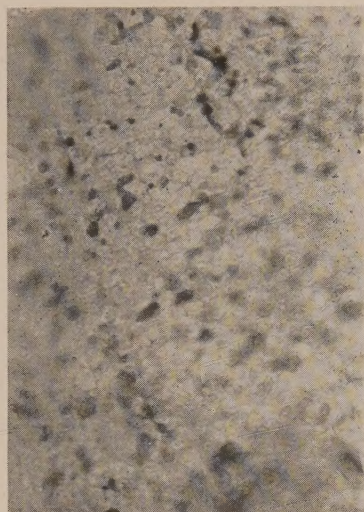


FIG. 4.—Case 2. Untreated vitiliginous area. Small, rounded, weakly DOPA-positive melanocytes. (Relative Type 1 vitiligo.) $\times 290$. DOPA.

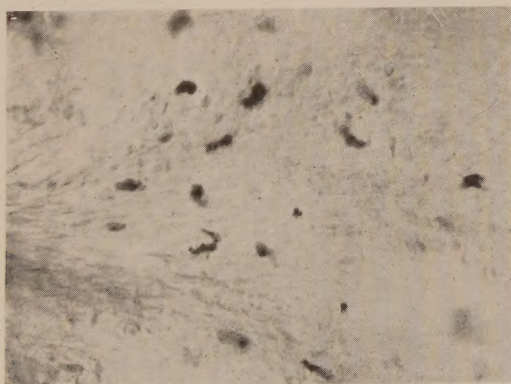


FIG. 5.—Case 2. Same area as Fig. 4 after treatment. Increased DOPA reaction of the melanocytes; no morphological or numerical change. $\times 290$. DOPA.

Case 3. A West African aged 20 years.

Vitiligo of the face, arms, and legs of 12 years' duration. The lesions were light brown and contrasted with his normal dark skin. One area on the right lower leg, however, was ivory white. Biopsies were taken from his normal skin, from one of the light brown patches, and also from the ivory white area.

This patient was treated for eight months with Meladinine and ultra-violet rays from a mercury vapour source, without any improvement. He was then treated with Meladinine and exposure to sunlight, and all the affected areas responded, except the ivory white patch. A fourth biopsy was taken from one of the repigmented areas.

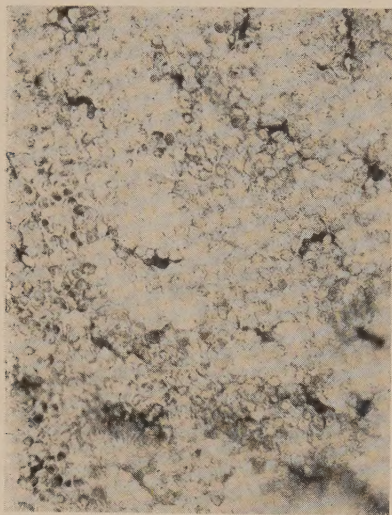


Fig. 6.—Case 3. Relative Type 2 vitiligo. Hypertrophied melanocytes and slight pigmentation of the Malpighian cells. $\times 223$. DOPA.

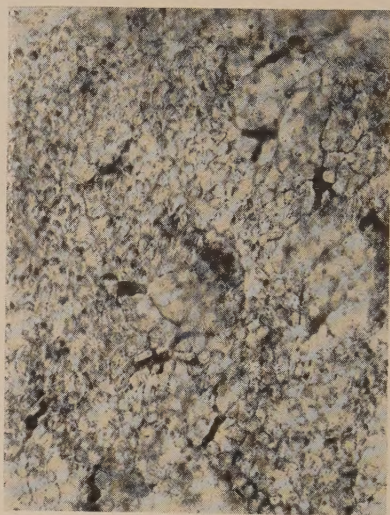


Fig. 7.—Case 3. Same area as Fig. 6 after treatment. Increased DOPA reaction of the melanocytes; no morphological or numerical change. There is a general increase of pigmentation of the epidermal cells. $\times 223$. DOPA.

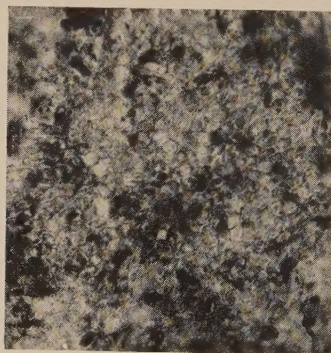


Fig. 8.—Case 3. Normal skin, showing normal melanocytes and deeply pigmented epidermal cells. $\times 223$. DOPA.

Histological findings.—The histology of the ivory white patch is identical with the absolute lesion illustrated in Fig. 2. The epidermal pattern is normal and surrounding the lesion are enlarged melanocytes similar to those depicted in Fig. 6. This patch did not repigment as a result of treatment.

The histology of a light brown area, before and after treatment, is shown in Figs.

6 and 7. A biopsy taken before treatment (Fig. 6) revealed the presence of DOPA-positive melanocytes throughout the lesion. These were of the enlarged type, but they were reduced in number in comparison with the surrounding skin (mean number in lesion 230 ± 30 ; mean number in normal skin 1050 ± 60). The basal layer of the epidermis was only slightly pigmented whereas in the normal area this was dark brown (Fig. 8).

The result of treatment with Meladinine and sunlight is shown in Fig. 7. The enlarged melanocytes became strongly DOPA-positive, but they did not increase in number or change their shape (mean number 270 ± 30). The basal layer of the epidermis also became heavily pigmented, indicating increased melanogenesis.



FIG. 9.—Area of relative vitiligo, showing hypertrophied melanocytes (Type 2) intermixed with small weakly DOPA-positive, Type 1 cells. $\times 290$. DOPA.

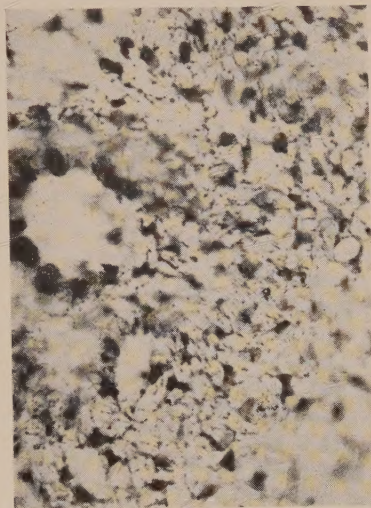


FIG. 10.— $\times 290$. DOPA.

This histological pattern of vitiligo, with a reduced number of DOPA-positive melanocytes, has been named "Relative Type 2" to distinguish it from Relative Type 1 vitiligo, where the melanocytes are present in normal numbers, but have a reduced tyrosinase activity.

A further case, a white man aged 43 years with early lesions, showed both types of relative vitiligo (Fig. 9). Both the large melanocytes (Type 2) and the small weakly DOPA-positive melanocytes (Type 1) are present in the same lesion. A normal area of this patient's skin is shown in Fig. 10. As this patient was seen during the winter months no treatment was given.

GENERAL CLINICAL OBSERVATIONS.

In European patients areas of vitiligo always appeared white. In dark-skinned patients most of the affected areas were light brown, contrasting with the normal darkly-coloured skin; ivory white lesions may be present in addition. Histological examination of lesions from coloured patients has

TABLE I.

Age (years).	Sex.	Race.	Duration (years).	Biopsies.		Histological type (biopsy site)	Treatment.		Response.	Remarks.
				Before treat- ment.	After treat- ment.		Mela- dine. (%).	Light.		
31	F	European	3	2	1	Absolute (thigh) (arm)	25	Sun	Acute erythema, blister- ing; no repigmentation.	No histological change after treatment.
				1	0	Relative Type 1 (shoulder)	—	—	—	—
37	F	European	8	3	2	Absolute (arm) (thigh)	12.5	Sun	Acute erythema, blister- ing; no repigmentation.	No histological change after treatment.
68	M	European	40	0	1	Absolute (chin)	100	Sun	Erythema; no repigmen- tation	Histology of absolute lesion after treatment.
43	F	European	3/12	2	0	Absolute (abdomen)	12.5	Sun	Erythema; no repigmen- tation	—
47	F	European	6	1 1	2 0	Absolute (arm) (back)	100	Sun	Erythema; no repigmen- tation	No histological change after treatment.
40	F	European	11	2	0	Absolute (thigh)	25	Sun	Blistering ++; slight perifollicular repigmen- tation	No satisfactory repig- mentation.
20	M	West African	12	1	1	Relative Type 2 (leg)	100	Sun	Repigmentation	Increased DOPA re- action of melanocytes.
				0	1	Absolute (ankle)	100	Sun	Erythema only	Histology of absolute lesion after treatment. (This patient had been treated with artificial U.V. and Meladine for 8 months with no effect.)

Age (years).	Sex.	Race.	Duration (years).	Histological type (biopsy site).	Biopsies.		Treatment.		Remarks.
					Before treat- ment.	After treat- ment.	Mela- dine (%).	Light. Sun .	
74	M	European	2	Relative Type 1 (arm)	2	2	50	Repigmentation	Increased DOPA re- action of melanocytes after treatment.
30	F	European	4	Relative Type 1 (arm)	1	0	50	Repigmentation	Rapid clinical response
56	M	European	4	Relative Type 2 (hand)	1	1	50	Clinical repigmentation	No definite histological changes after treat- ment.
24	M	West African	2½	Relative Types 1 and 2 (thigh)	1	0	100	Repigmentation	Repigmentation was temporary.
24	F	European	9	Absolute (hand)	1	0	100 and by mouth	U.V. . No response	Patient had a contact eczema of hands, therefore local treat- ment stopped.
53	F	European	1	Absolute (thigh)	2	0	—	—	Patient seen during winter months.
43	M	European	1	Relative Types 1 and 2 (arm)	1	0	—	—	Patient seen during winter months.

indicated that this variation in colour corresponds to different types of vitiligo. The ivory white patches are areas of Absolute vitiligo, and the light brown patches are Relative types. Although the same variations exist in white patients, they are all the same colour clinically and can only be distinguished histologically.

All cases of vitiligo except the Absolute lesions of a negro tended to become less obvious during the winter months. For this reason care has to be taken in interpreting the results of treatment at this time. In the spring, the differentiation between the lesions and the normal skin again becomes noticeable.

Results with Meladinine and artificial irradiation.

About twenty vitiliginous areas on four patients were painted once or twice during the week, and exposed twice weekly to artificial ultra-violet rays from a mercury vapour lamp. Three of these patients had absolute vitiligo, and one had a Relative Type 2 lesion (Case 3). None of these patients responded to treatment; there was no evidence of repigmentation even after eight months' therapy. There were no severe reactions as a result of this treatment; only a mild erythema developed on the treated patches.

Results with Meladinine and solar irradiation.

The results obtained when patients were exposed to natural sunlight were more satisfactory. In some of these, repigmentation occurred, and this was observed in one case of relative vitiligo who had previously failed to respond to artificial irradiation (Case 3). The absolute variety failed to repigment, but the relative types responded. This repigmentation was not permanent and after several months a further course of treatment was often required.

With this treatment reactions were more severe than with artificial irradiation; some of the cases of absolute vitiligo developed severe erythema and blistering, and treatment had to be abandoned.

TABLE II.—*Patients treated, no biopsy taken.*

Age (years).	Sex.	Race.	Duration (years).	Clinical type.	Treatment.		Response.
					Mela- dine (%).	Light.	
26	M	Indian	5/12	Relative	100	Sun	Repigmented, but relapsed; given further treatment.
36	F	European	2½	Absolute	25	Sun	Erythema ++ no repigmenta- tion.
8	F	European	2/12	Absolute	12.5	Sun	Erythema ++ no repigmenta- tion: hyperpigmentation of normal skin.
24	M	West Indian	2	Relative	100	Sun	Repigmented; relapsed after 3 months, given further treatment.

Details of the fourteen cases of vitiligo on whom biopsies were performed are given in Table 1. The types of vitiligo are listed, and their response to treatment shown. No area of absolute vitiligo responded or showed any histological change. The clinical results obtained in those cases in which no biopsies were performed are recorded in Table 2.

Experimental observations on the effects of Meladinine and sunlight on normal skin and on vitiliginous skin.

In one case of absolute vitiligo a round area including both normal and vitiliginous skin was painted with Meladinine and exposed to sunlight. On the vitiliginous area only an erythema developed, while the normal skin became hyperpigmented. Biopsies were taken from the painted and unpainted normal skin, and also from the painted and unpainted vitiliginous skin. In the area of absolute vitiligo no DOPA-positive melanocytes were present, and no change had occurred in the painted and irradiated portion. On the painted and irradiated normal skin there was a marked increase of the DOPA reaction of the melanocytes, but there was no significant increase in their number. (Normal skin, painted and irradiated: mean number of melanocytes per sq. mm. 2600 ± 100 . Normal skin, irradiated but *not painted*: mean number of melanocytes per sq. mm. 2400 ± 90 .)

DISCUSSION.

Theoretically, the absence of melanin in the epidermis could be due to anatomical or to physiological changes. Anatomically, melanocytes might be reduced in number or they may be completely absent. This anatomical deficiency has, however, never been clearly demonstrated in man, since these dendritic cells can be shown to be present even when they fail to produce melanin.

Physiologically, melanogenesis could be affected in several ways. There could be an absolute or relative inhibition of tyrosinase; the supply of substrate, tyrosine, could be insufficient or the biophysical process of the formation of melanin granules could be defective; lastly, the transfer of melanin granules into the neighbouring Malpighian cells (cytocrine action, Masson 1948) could be impaired. All or any one of these factors could produce leucoderma.

Our investigation indicates that there are several variations in the pathology of vitiligo. Previously it was thought that vitiligo was a single pathological entity characterized by complete absence of DOPA-positive melanocytes.

Absolute vitiligo is due to a total absence of tyrosinase activity and corresponds to the pathology already described by Bloch (1917*b*, 1929), and confirmed by Laidlaw (1932) and Becker (1933). We have confirmed the findings of Becker (1933) and of Becker *et al.* (1952) that melanocytes are still present in these

lesions, but that they are DOPA-negative. These cells can be demonstrated with paracarmine, or supravital staining with methylene blue. It is not known whether the DOPA-negative melanocytes are as numerous as the DOPA-positive cells in the neighbouring normal skin. Neither paracarmine nor methylene blue was found reliable enough for an accurate estimate.

We have been able to demonstrate two other types of vitiligo, and these we have called the relative vitiligos. In Relative Type 1 the number of melanocytes is unaltered, but their tyrosinase activity is reduced. Clinically the skin is still pigmented, but it is of a lighter colour than normal. In the Relative Type 2 vitiligo, there is a reduction in number of the DOPA-positive melanocytes, and those remaining are enlarged and have very long dendritic processes. It seems that this is a functional hypertrophy of the remaining DOPA-positive cells in an attempt to maintain the pigmentary level of the affected skin. Enlarged melanocytes are not peculiar to vitiligo and have been observed in other conditions, such as scars, where the number of functioning melanocytes has been reduced (Szabó, unpublished). Moreover they are generally found at the periphery of *any* type of vitiliginous lesion, and have been already described by Laidlaw (1932). As a result of treatment of Relative Type 2 vitiligo with Meladinine and sunlight, these enlarged melanocytes become more active, as shown by an increased DOPA-positivity, and this is no doubt responsible for the clinical repigmentation.

The histology of Relative Type 2 vitiligo is identical with the changes found at the edge of a patch of absolute vitiligo. Perhaps the tyrosinase activity of the melanocytes is at first reduced, and the normal cells at the edge of the area enlarge: later there is a complete loss of enzyme activity at the centre, so that absolute vitiligo arises as the end result of a gradual process.

More than one type of lesion can occur in any individual patient. Absolute and relative vitiligo can be easily distinguished histologically in all races, but the distinction is clinically possible only in dark-skinned patients. The prognosis of absolute vitiligo is bad, but moderate though temporary improvement can be obtained in the relative types. Treatment of absolute vitiligo often results in severe blistering, probably as a result of complete lack of protection against sunlight in skin that has been rendered sensitive by Meladinine. Even if some of the melanocytes were capable of revival, the severe reaction and subsequent destruction of the epidermis would eliminate them.

The existence of several variations in the histology of vitiligo, and the fact that Meladinine is more effective with sunlight than with artificial ultra-violet rays (Kanof, 1955, and our own cases), explains the varied results in the literature regarding the success of Meladinine therapy. The importance of the source of radiation employed after Meladinine painting is emphasized by our unpublished experiments with guinea-pigs. We found that albino guinea-pigs, treated with Meladinine both locally and systemically, pigmented more readily

with x-rays than with Grenz irradiation. (This is incidentally one indication that we can no longer draw a sharp distinction between the chemical mode of action of ultra-violet rays and the physical action of x-rays).

As a result of treatment, repigmentation occurred only in those lesions in which the melanocytes still retained some tyrosinase activity. The number of DOPA-positive melanocytes in a repigmented area was not significantly higher than before treatment and we did not observe any evidence of cell migration at the edges of the lesions. It seems unlikely that there is an invasion of the affected area by DOPA-positive melanocytes from the adjacent normal epidermis.

In all types of vitiligo, the normal skin at the edge of a lesion became hyperpigmented as a result of treatment. It is possible that the increased activity of the melanocytes in this hyperpigmented border stimulated the less DOPA-positive melanocytes within the lesion. This action of one melanocyte upon another had been described as "pigment spread" by Billingham and Medawar (1948).

Racial factors may have some relation to the pathogenesis of vitiligo. In our series all the coloured patients responded to treatment, whereas the majority of lesions in European patients were absolute and failed to repigment. Vitiligo seems to affect the melanocytes of the European more severely, especially those of the Nordic type, whose skin is very lightly pigmented. The actual number of melanocytes is similar in coloured and white races (Billingham, 1949) but in the former they are more active and less easily inhibited. Similarly albinism, a congenital absence of tyrosinase activity of the melanocytes throughout the body, when it affects Africans tends to be incomplete. The eyes in these subjects are often blue, and the skin freckled (Barnicot, 1952).

SUMMARY.

Patients with vitiligo were treated with Meladinine and exposure to either artificial ultra-violet rays or sunlight.

Three types of vitiligo have been demonstrated histologically :

- (i) Absolute, in which no DOPA-positive melanocytes are present.
- (ii) Relative Type 1, in which the melanocytes are very slightly DOPA-positive, but are present in normal numbers.
- (iii) Relative Type 2, in which the number of DOPA-positive melanocytes is reduced. Throughout the lesion, these remaining cells are enlarged and have elongated dendritic processes. The border zone of *all* types of vitiligo is characterized by such hypertrophied melanocytes.

It is possible that the pathogenesis of these three types is related, the Relative types being a forerunner of the Absolute. Not all lesions, however, progress to the Absolute stage.

Repigmentation occurred only when Meladinine painting was followed by solar irradiation ; artificial ultra-violet rays were unsatisfactory.

Only the relative vitiligo became repigmented as a result of treatment. This response was due to stimulation of the remaining DOPA-positive melanocytes, and not to any increase in their number.

Absolute vitiligo did not improve with treatment. The DOPA-negative melanocytes were not capable of being activated by treatment.

Generally, the prognosis is more favourable in coloured than in white races. The former usually have the relative types of lesions ; but even in these cases repigmentation appears to be temporary.

We wish to thank Dr. W. N. Goldsmith, Prof. R. J. Harrison, Prof. P. B. Medawar F.R.S., Prof. W. Montagna, and Dr. Brian Russell for their interest and advice with this investigation. We are also grateful to Mr. W. Brackenbury of University College, London, for the photomicrographs.

REFERENCES.

- BARNICOT, N. A. (1952) *Ann. Eugen., Lond.*, **17**, 38.
 BECKER, S. W. (1927) *Arch. Derm. Syph., Chicago*, **16**, 259.
 — (1933) *Ibid.*, **28**, 497.
 BECKER, JR., S. W., FITZPATRICK, T. B. and MONTGOMERY, H. (1952) *Ibid.*, **65**, 511.
 BILLINGHAM, R. E. (1948) *J. Anat., Lond.*, **82**, 93.
 — (1949) *Ibid.*, **83**, 109.
 — and MEDAWAR, P. B. (1948) *Heredity*, **2**, 29.
 — (1953) *Phil. Trans., B.*, **237**, 151.
 BLOCH, B. (1917a) *Hoppe-Seyl. Z.*, **98**, 226.
 — (1917b) *Arch. Derm. Syph., Wien*, **124**, 209.
 — (1929) *Amer. J. med. Sci.*, **177**, 609.
 EL MOFTY, A. M. (1948) *J. Egypt. med. Ass.*, **31**, 651.
 GEORGE, W. M. and BURKS, JR., J. W. (1955) *Arch. Derm. Syph., Chicago*, **71**, 14.
 — (1955) *Ibid.*, **72**, 458.
 KANOF, N. B. (1955) *J. invest. Derm.*, **24**, 5.
 KISSMEYER, A. (1920) *Brit. J. Derm. Syph.*, **32**, 156.
 LAIDLAW, G. F. (1932) *Anat. Rec.*, **53**, 399.
 LERNER, A. B., DENTON, C. R. and FITZPATRICK, T. B. (1953) *J. invest. Derm.*, **20**, 299.
 MASSON, P. (1948) *Pigment Cells in Man*. In *The Biology of Melanomas*, p. 15. (Special Publications of the New York Academy of Sciences, vol. 4.) New York : The New York Academy of Sciences.
 MEDAWAR, P. B. (1941) *Nature, Lond.*, **148**, 783.
 — (1953) *Quart. J. micr. Sci., N.S.*, **94**, 481.
 PEGUM, J. S. (1955) *Brit. J. Derm.*, **67**, 348.
 SIDI, E. and BOURGEOIS-GAVARDIN, J. (1951) *Bull. Soc. franc. Derm. Syph.*, **58**, 490.
 SZABÓ, G. (1954) *Brit. med. J.*, **i**, 1016.
 — (1955) *J. Path. Bact.*, **70**, 545.

TREATMENT OF CONTACT SENSITIVITY TO ANTIBIOTICS AND RELATED SUBSTANCES IN NURSES.

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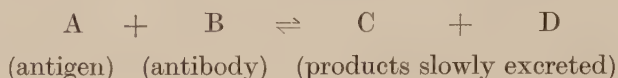
The United Birmingham Hospitals.

It is well known that the development of contact sensitivity to chemotherapeutic and antibiotic agents and to local anaesthetics is an occupational hazard of nurses and doctors. Since the first papers on sulphonamide dermatitis before the war, many cases of penicillin and streptomycin sensitivity have been published, culminating in a report from the Ministry of Health (1953) which chiefly contained recommendations for prophylaxis. Although the local public health authorities were aware of the risks, and some hospitals had already taken preventive measures on their own initiative, these were not enforced throughout the United Birmingham Hospital group, and the following observations are based on a small number of cases drawn from the student nurses at the Queen Elizabeth Hospital and from industrial and district nurses in the Birmingham area who were found to have developed sensitivity to penicillin, procaine, streptomycin and in one case chloromycetin, and where desensitization by oral administration was attempted.

Desensitization to penicillin by the subcutaneous and intramuscular route was achieved by Alexander (1953) but as long ago as 1946 O'Donovan and Klorfajn had reported one case successfully desensitized by the oral route. Cohen and Glinsky (1951) were the first to record desensitization to streptomycin, and Crofton (1953) reported success in two cases by subcutaneous or intramuscular injection. I can find no report of attempted desensitization to chloromycetin or procaine, although Bercke and Obermayer (1948) noted that hypersensitivity to procaine developed in nurses who used it to relieve the pain of streptomycin injections, and sensitivity to the procaine molecule in procaine penicillin has been reported. The incidence of this condition cannot be assessed with any accuracy, but Marcussen (1949) showed that for streptomycin there was a correlation between the development of sensitivity and the degree of exposure over a period of time.

The clinical picture is well recognized, as are the limitations and fallacies of patch tests. However, these were used as an index of epidermal sensitization, both to establish the diagnosis and later as a guide to the effectiveness of desensitizing measures. Neither penicillin nor streptomycin are primary irritants, but in order to avoid false positive patch-test results in eczematous subjects serial dilutions were used, down to about 1%.

Treatment by desensitization is indicated where sensitivity is high and contact is likely to continue indefinitely. If the antibiotic is absorbed by mouth the oral method, though slower than parenteral methods, has obvious advantages where so many doses are needed. Treatment is based on the assumption that antigen and antibody and the products of their interaction behave according to the Law of Mass Action as expressed in the following formula :



In the sensitized subject, after drug contact has ceased and time has been allowed for excretion of the products of the reaction, all that remains is B. If now A is given by mouth, the reaction moves to the right then slows to equilibrium. With C and D slowly eliminated and A constantly given, the reaction proceeds slowly to the right until B is exhausted and desensitization is then complete. Tate and Klorfajn (1944 *a* and *b*) discuss the theoretical basis of this method in detail in connection with sulphonamide dermatitis and no further reference will be made to it here. In practice, each case is an individual problem, but the higher the degree of sensitivity the smaller the initial desensitizing dose must be and the more gradual the increments. In very sensitive patients the doses are covered by an antihistamine. No serious reactions, either local or general, have been encountered.

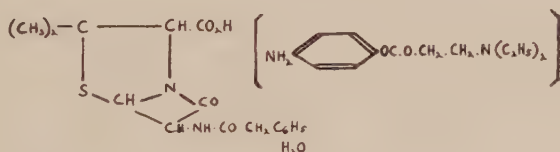
For *Penicillin* the initial dose is 50 Oxford units of crystalline penicillin G by mouth, working up daily with early increments of 100 to 150 O.u. a week, later increasing to a maximum of several thousand O.u. a day over a period of 8 to 12 weeks. A test dose of 50,000 O.u. three times a day for one day is then given, followed in ten days by a patch test. Desensitization has been successful in 7 out of 9 cases so treated. The better oral absorption claimed for the recently introduced acid-resistant phenoxymethylpenicillin should make this method more reliable and this preparation is now being used.

Occasionally suspected sensitivity to penicillin is found to be due to the *procaine* radicle. Procaine, an ester of *p*-aminobenzoic acid, belongs to the large group of drugs with a primary aromatic amine structure which includes the sulphonamides, *p*-aminosalicylic acid and paraphenylenediamine many of which are known sensitizers (Fig. 1). Cross sensitization between members of this group is probably not uncommon; there may be an exquisite degree of specificity directed to one part of the molecule or there may be occasionally, as in Marsh's case (1952), sensitivity to five distinct compounds within the related group. Our knowledge of the mechanism of delayed hypersensitivity, especially of contact type, is incomplete, and it is well known that patients who become spontaneously sensitized to one substance may react non-specifically

when their irritable skins are challenged with other antigens; furthermore, people handling many drugs may become independently sensitized to two or more related compounds. Nevertheless, Rostenberg and Kanov's work (1945) on deliberately induced sensitization shows that true cross-sensitization can indeed occur to substances which are stereochemically similar and which can form similar conjugates.

In patients sensitive to procaine, therefore, cross-desensitization was attempted with a closely related compound which could be taken by mouth, namely sulphanilamide, which was chosen as the simplest structure, and the least liable to give side effects. Starting with 0.0625 g. ($\frac{1}{8}$ tablet) twice daily, the dose is gradually increased over a period of 8 to 12 weeks until 0.5 g. twice

PROCAINE PENICILLIN



SULPHANILAMIDE



FIG. 1.

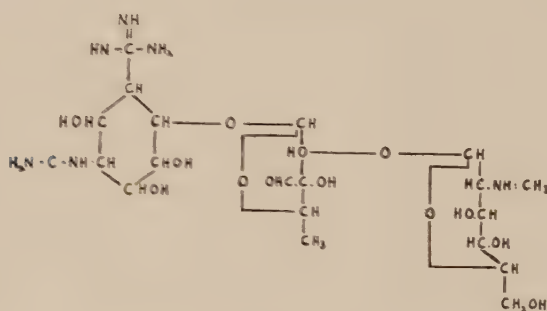
or three times a day is tolerated. After a final test dose of 1 g. three times a day, a patch test is repeated in ten days. This method has been successful in three cases.

Cases of *streptomycin* sensitivity cannot be desensitized by oral administration since the drug is not absorbed. Structurally streptomycin contains three separate moieties (streptidine, streptose and N-methyl L-glucosamine) joined by saccharide linkages (Fig. 2). Streptidine, which has a central benzene ring structure with amino groups loosely attached, has therefore a certain resemblance to the procaine series. The possibilities of cross desensitization were further exemplified by a case highly sensitive to both streptomycin and chloramphenicol. Desensitization to chloramphenicol was attempted first, starting with 25 mg. daily and increasing to a final dose of 625 mg. After a rather protracted course of 7 months, due to frequent slight local reactions, patch tests were then found to be negative to both chloramphenicol and streptomycin. Chloramphenicol has the same ring structure as the

sulphonamide-procaine series, with a nitroso group replacing the amino group in the para position, but was considered unsuitable for routine use. Accordingly, in a subsequent case sensitive to streptomycin and procaine, desensitization to both was attempted with sulphanilamide: the procaine sensitivity was abolished but the streptomycin sensitivity, although reduced, was still present.

In the light of further experience, it now seems probable that cross-desensitization to streptomycin by the oral method is most likely to succeed when the patient happens also to be sensitized to a drug of related structure which can be given by mouth, or when the degree of sensitivity is not too high.

STREPTOMYCIN



CHLORAMPHENICOL



FIG. 2.

Highly sensitive subjects will respond best to desensitization by graded intramuscular injections, starting with very small doses of the order of 1 to 10 micrograms. Five such cases have been successfully treated.

The results in this small group of cases have been encouraging as judged by freedom from rash, a negative patch test and the ability to take a large oral dose without any local reaction. The permanency of desensitization, by whatever route, still remains most difficult to assess. Most nurses have taken precautions in their future handling of all antibiotics, and in hospital may continue the intensive contact which seems to be a prerequisite for the development of sensitization for only a limited time, say 12 months, during their training. The majority in this series had in the past had minor trouble with their skins from institutional soaps, blankets, disinfectants and the like, and in those cases where a contact type rash has recurred after successful desensitization other factors must have been responsible since either patch tests

have remained negative or contact with antibiotics has ceased. This brings antibiotic sensitivity into line with the majority of so-called occupational eczemas, in that it mainly occurs not as an isolated event but as an episode in a history of recurring rashes due to the action of trauma and primary irritants on a skin constitutionally sensitive or rendered vulnerable by endogenous factors.

SUMMARY.

Nurses sensitized by contact with antibiotics have been desensitized by an oral method.

Cross-sensitization within the group of antibiotics and related compounds is discussed, and treatment by oral cross-desensitization is recommended in selected cases.

I wish to thank Dr. B. C. Tate for permission to study his cases and for much helpful advice.

REFERENCES.

- ALEXANDER, L. J. (1953) *Arch Derm. Syph., Chicago*, **68**, 323.
BERKE, M. and OBERMAYER, M. E. (1948) *J. invest. Derm.*, **11**, 253.
COHEN, A. C. and GLINSKY, C. G. (1951) *J. Allergy*, **22**, 63.
CROFTON, J. (1953) *Brit. med. J.*, *ii*, 1014.
MARCUSSEN, P. V. (1949) *Acta derm.-venereol., Stockh.*, **29**, 410.
MARSH, K. (1952) *Lancet*, *ii*, 606.
O'DONOVAN, W. J. and KLORFAJN, I. (1946) *Lancet*, *ii*, 444.
ROSTENBERG, Jr., A. and KANOF, M. N. (1945) *J. invest. Derm.*, **6**, 201.
'Sensitization of Nursing Staffs to Antibiotics' (1953) *Brit. med. J.*, *ii*, 30 ; 39.
TATE, B. C. and KLORFAJN, I. (1944a) *Lancet*, *i*, 39.
——— (1944b) *Ibid.*, *ii*, 553.

CHLORPROMAZINE DERMATITIS IN NURSES.

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TIME spent in the investigation of contact dermatitis is always rewarding, as removal of the offending antigen usually results in complete cure.

The patients in this article were all from the Moor Hospital, Lancaster, and included ten part-time trained mental nurses, one full-time male mental nurse and a pharmacist, who presented as cases of contact dermatitis which was found to be caused by handling Largactil (chlorpromazine hydrochloride). Most of them had made their own diagnosis and several had attempted to avoid contact before they were seen. At the first interview a full history was taken and clinical examination made, patch tests were carried out and clear instructions given on how to avoid contact. Follow-up examinations were arranged during the subsequent nine months.

The *clinical picture* was typical of contact dermatitis. The onset in five out of the twelve patients was on the face with redness, swelling and sometimes weeping of the skin, especially around the eyes, but also about the mouth. The other seven cases presented with the rash in the clefts or on the sides of the fingers. After the acute reaction had subsided there remained a dry scaling dermatitis which cleared up completely when the patient went sick or on holiday (provided she avoided the sun) but usually relapsed on return to the same ward. One nurse had a tablet spat at her left eye by an insane patient. The area started to irritate nine hours later and when she woke up next morning, nineteen hours after the incident, all the skin around the eyes was red and so swollen as to interfere with vision; there was still some swelling and deep red colour when she was examined three days afterwards.

DISCUSSION.

A surprising fact is that only one male nurse was affected. In a small personal series of female patients, proved by patch tests to be sensitive to nickel-plated steel suspenders, it was found that in nearly half the onset was within two years of the menopause. Five out of ten of the nurses came within this age period, but no definite conclusion can be drawn from this as the average age of the whole female nursing staff is 45. Dr. P. H. Mitchell has indicated that because the Largactil treatment of certain chronic psychoses seems to be more effective in female patients than in males, the tendency is to

give it more frequently to women and it is therefore the female nurses who have to handle it more often. Also the total female staff numbers 429 and the male 147, and this will accentuate the difference. In the women's wards the tablets were usually crushed between spoons and dissolved in boiling water, and from the histories of contact this would account for at least seven cases. Crushing was not carried out by the male nurses and this appears to be one of the factors responsible for the low incidence of dermatitis among them.

It is interesting to note that all the five patients who presented with swelling of the skin around the eyes were those who did not wear glasses at work, had strong patch-test reactions and had been crushing tablets. Photo-sensitivity is another definite factor and was noticed by at least five out of the twelve patients and in all these the skin around the eyes was affected. Four patients flared on exposure to the sun when away on holiday. This occurred in the first patient encountered in June 1955 and led to some doubt as to the correct diagnosis until patch tests were performed. Swelling of the skin of the face and particularly of the lower lip and around the eyes was noted by Dr. H. C. Fisher in four male mental patients after they had been in the sun for three days for four hours daily, when the drug was being given systemically. Unfortunately the other mental patient examined with a similar rash had treated herself with pepper but the distribution of the rash was obviously actinic.

Finding the correct strength for patch-test solutions is always difficult as quite often the recommended figure gives false positive reactions in patients suffering from eczema. In the present series all the cases were positive to 0.66% solution of Largactil powder and only two were negative to 0.1% solution. A widespread relapse of the rash was encountered in two patients after patch-testing. The importance of reading the tests at ninety-six as well as at forty-eight hours when the patches are removed cannot be emphasized too much, since nine out of ten of the 0.1% and seven out of twelve of the 0.66% tests gave delayed positive results. The patch-test solutions should be freshly prepared from Largactil powder and put in dark bottles.

The Largactil preparation available for intravenous injection is unsuitable for patch-testing. This was clearly indicated by the results of a control series of four non-eczematous cases in the skin in-patient unit of another hospital where Largactil was not being used at the time; one gave a false positive reaction to 1%, as did three out of five eczema patients tested prior to discharge, despite the fact they had never had the drug before. On the other hand, seven eczema patients were all found to be negative to 0.66% solution made from the powder. The number of control cases is small as it was not felt justified to ask for volunteers from nurses and doctors because of the risk of subsequent occupational sensitization.

In only one case in the series was the diagnosis at first in doubt because the patient presented as patchy eczema of the hands and fingers. There was a

definite history of the rash starting on the finger-tips used to handle the tablets and eventually the rash involved the skin around the eyes ; it was after patch tests that the finger clefts became typically affected. This patient can perhaps be considered a case of constitutional eczema precipitated originally as contact dermatitis for she is the only one in the series who still has persistent skin trouble after a period of nine months follow-up. During this time seven patients have remained clear, two patients have had two relapses and two have had single ones, all of short duration ; it is interesting to note that three of the four relapse cases had strongly positive patch-test reactions to 0.1% solution. Apart from the patient with eczema mentioned above the rest recovered within a few weeks of following instructions concerning a rigid " no touch technique ". It was advised that Largactil tablets should be given with clean spoons and that the nurses should wash afterwards ; alternatively, rubber gloves had to be worn. It was recommended that unco-operative patients should receive Largactil by injection, the nurses wearing rubber gloves, masks and gowns, and avoiding droplet spray into the atmosphere by inserting the needle into a large piece of sterile cotton wool when removing the air from the syringe. Crushing or dissolving tablets was forbidden and the use of syrup or solution of Largactil discontinued. Perhaps the best way of impressing the nurses with the need for care is by asking them to handle the drug as if it were mustard gas.

All this emphasis is needed as contact with the minutest quantity of the drug will cause relapse. One female mental patient, aged 65, developed contact dermatitis of the flexor aspects of the wrists, forearms, the backs of the hands and fingers with typical involvement of the finger clefts. She made the beds of patients in a ward where Largactil was being given and was found to be positive to 0.1% solution, having never taken the drug previously ; no other possible cause for her rash could be found. The degree of sensitivity is also shown by the pharmacist who relapsed after unpacking but not opening tablet containers. (Psychological factors can be excluded as he did not know the diagnosis at the time.) Sugar-coating the tablet is not a sufficient protection, for in two cases the rash first appeared on the tips of the fingers used to hand them out to patients.

The original patch tests were carried out with the intravenous solution and consequently had to be repeated. As all were still positive after a period of nine months, it was decided to advise the medical staff to arrange for a ward to be occupied by patients who never have Largactil and for the very sensitive nurses, who have relapsed, to work there. If a patient in this ward needs the drug she is transferred elsewhere. It is too early to say how this will work.

Nine cases were patch-tested to a fresh 1% solution of Pacatal which Mr. A. K. McIver, Group Pharmacist at Barrow, had noted was, like Largactil, a phenothiazine derivative, and was not supplied in sugar-coated tablets. Three

of the tests were positive (one being delayed), indicating that cross-sensitivity exists between the two drugs.

Since the investigation of the original twelve cases only four more female nursing staff have developed Largactil dermatitis and all of them had not been carrying out instructions (one of them had been putting the tablets on the spoons with her fingers). The diagnoses were confirmed by patch tests but these cases have not been included in the series as they have only been followed up for three months though all are now free from skin trouble.

SUMMARY.

Twelve cases of contact dermatitis from handling Largactil (chlorpromazine hydrochloride) are described and the clinical picture is given briefly.

The degree of sensitivity makes it difficult for contact to be avoided unless detailed instructions are given personally.

Methods of prevention are suggested.

Photo-sensitivity is established as a contributory factor in causing the dermatitis. Cross-sensitivity to Pacatal is reported.

I should like to thank the Medical Staff, the Matron and the Chief Male Nurse of Moor Hospital for their interest and co-operation; Sister Ayres and Sister Morrison for carrying out the patch tests; Charge Nurse Taylor, Miss Hetherington and Miss Hirst for their help at the treatment centre; and Dr. Robert Forgan, Chief Medical Adviser to Messrs. May & Baker Ltd., for the Largactil powder.

ROYAL SOCIETY OF MEDICINE.

SECTION OF DERMATOLOGY.

President—DR. LOUIS FORMAN.

15 December 1955.

Poikiloderma Congenita.—Dr. ARTHUR ROOK and Dr. R. A. DAVIS.S. G—, a boy aged $2\frac{1}{2}$ years.

An only child of healthy and unrelated parents with no history of any similar condition in the family.

The pregnancy was of full term and was normal throughout. The infant's birth-weight was 4 lb. $1\frac{1}{2}$ oz. He thrived well, was weaned at 5 months, spoke his first words at 1 year and walked at 14 months. He has always been fit and active. The teeth have erupted normally. Red blotchy patches appeared on the cheeks quite suddenly at the age of 18 months, and increased in size to involve the nose, forehead, chin and the tips of the ears. One month later similar patches appeared on the backs of the hands and forearms. They were more noticeable when the child cried or after exposure to sunlight. They have faded slightly during the past few months.

On Examination (25 November 1955).

The child is very small for his age (height 2 ft. 3 in. weight 15 lb.) but is well proportioned. The features are pointed. There is no apparent mental retardation.

Skin.—The face shows symmetrical reticulate pigmentation and telangiectasia, with fine scaling, affecting the cheeks and the glabella, extending laterally to the preauricular regions and the tips of the ears, and downwards to the angle of the mandible and the chin. The lips and eyelids are spared. On the forehead and on the extensor surfaces of the forearms is a faint macular pigmentation. There is no clinical atrophy. The scalp hair is normal and the cheeks and back show a strong growth of lanugo hair.

When the child was first examined on 22 August 1955, all the lesions were more conspicuous and active erythema accentuated the reticulate pattern of those on the face. On the back of the left hand and forearm were numerous lichenoid papules in an irregularly reticulate arrangement and the follicles were uniformly prominent, some showing hyperkeratosis. The teeth are normal. The palate is narrow and highly arched. The eyes are normal and no clinical abnormality is present in any other system, other than the absence of the left testis from the scrotum and inguinal canal.

Skiagram.—No abnormality in the secondary teeth or in the skull or pelvis.

Blood count within normal limits. Serum total proteins 8.0 gm./100 ml.

Comment.

Some 40 cases have now been reported as Rothmund's syndrome, Thomson's syndrome or poikiloderma congenita. Maeder (1949) accepts as examples of Rothmund's syndrome only those patients in whom a juvenile cataract has developed. However, there are records of patients reaching adult life without cataracts in the same families as cases presenting the complete syndrome. There appear to be no

good grounds for separating, merely on the presence or absence of ocular lesions, two syndromes that are otherwise identical. The variations from case to case are no greater than one encounters in other complex congenital syndromes.

An interesting feature in our patient is the light sensitivity. This was particularly noted in one of Brain's patients (1952) and in two of the six described by Sexton (1954), in whom sunlight provoked blister formation. It has been pointed out that the clinical and histological appearance of the skin of these patients as they grow older may very closely resemble xeroderma pigmentosum (Rook and Whimster, 1949).

REFERENCES.

- BRAIN, R. T. (1952) *Proc. Xth Internat. Cong. Derm.*, London; p. 531.
 MAEDER, G. (1949) *Ann. Oculist.*, Paris, **82**, 809.
 ROOK, A. J. and WHIMSTER, I. W. (1949) *Brit. J. Derm.* **61**, 197.
 SEXTON, G. B. (1954) *Canad. med. Ass. J.*, **70**, 662.

Acquired Epidermolysis Bullosa.—Dr. ALLISON (for Dr. F. RAY BETTLEY).

A man aged 25 years.

History.—In 1951 he developed eczema of his hands. This healed after treatment with x-rays in August 1952. In December 1952, he noticed for the first time that slight trauma resulted in blistering of the skin. The blisters occurred only on the hands, not in the mouth or on the feet. He remained well apart from this symptom.

There was no significant past or family history.

Examination of the backs of the hands and fingers showed many scars, the older being darkly pigmented, the more recent being pink. One of the older scars contained milia. In addition two fresh thick-walled pear-shaped blisters each about 1 cm. long were present at the base of the left thumb.

Histology showed a subepidermal bulla. There was some fragmentation of the elastic tissue. Examination of the urine for porphyrins showed none to be present.

Comment.—This case was taken to represent the rare acquired form of epidermolysis bullosa. The degree of dystrophy was minimal and comprised residual permanent scarring without associated nail changes.

Dr. H. HABER: Histologically it is epidermolysis bullosa.

Dr. G. C. WELLS: I do not think that you can conclude from the histology alone that this is epidermolysis bullosa. If this were a case of porphyria with blisters from trauma or light sensitivity, one might expect to see in the section a subepidermal bulla with little or no inflammation in the dermis, just as in this case.

Case of Senear-Usher Syndrome.—Dr. E. N. M. JOHNSTON (for Dr. E. W. PROSSER THOMAS).

Mr. D. J. L—, aged 22.

History.—In 1953 this patient noticed on the pre-sternal and inter-scapular regions crusted patches which have persisted and increased in number on other parts of the upper trunk. There have been episodes of blistering with watery discharge from the ruptured blisters. There is no family history of similar eruptions.

Examination.—General condition excellent. In the pre-sternal and intrascapular regions there are a small number of crusted warty greyish brown patches with well defined borders. Erythema is present in some of the lesions.

Histology.—Dr. Haber reports the histology shows characteristic features of pemphigus foliaceus (Senear-Usher syndrome).

Dr. H. HABER: The histology shows acantholysis in the region of the stratum granulosum and is diagnostic of Senear-Usher syndrome, pemphigus foliaceus and fogo selvagem.

Dr. ARTHUR ROOK: Have you any ideas of prognosis in such cases? We have a similar one in a girl aged 20; she has the lesions on the face and chest. I am unwilling to give her ACTH or cortisone. In Scandinavia two such cases responded to Germanin (Flodén, C. H., and Gentile H., 1953, *Acta derm.-venereol.*, Stockh., **33**, 402). I gave her a course, but there was no response. Is it wiser to withhold the corticosteroids?

Dr. G. B. DOWLING : I would support the idea of withholding treatment with cortisone at this stage which does not interfere greatly with the patient's health and which may persist for years. It appears to be impossible to foretell with certainty in which direction these cases are going to develop, though the majority evidently become foliaceous rather than bullous. It seems right to wait until development in one direction or the other has taken place. We are in difficulty at present over a patient of this kind at St. John's Hospital who has recently developed blisters in the mouth. This we think may mean that we ought to begin treatment.

The PRESIDENT : I think that is true. I have two of these patients; both of them have developed flat blisters, but the blisters in the mouth have not been of a size to enable a definite diagnosis of foliaceous to be made.

Both my patients have been on cortisone. One was a young woman who wanted to get married and one felt one would like to help her. She did improve, but she needed considerable dosage, enough to make her put on weight and become cushiony. She has married and is very pleased with herself.

The second was a patient in whom the lesions were very much of this type, some of them more warty and horny than most of the lesions; it became extremely severe and widespread, over the scalp, face, trunk with occasional blisters on the finger tips and mouth. She was very distressed about it and we put her on to cortisone but it did not respond. We have cut the dosage down and a hydrocortisone ointment on the face was abandoned. I agree it depends entirely on the severity of the eruption. They are best not treated with cortisone.

Dr. HELLIER : In my experience this type of pemphigus is more difficult to control than other forms.

Epidermodysplasia Verruciformis with Dysplasia of the Lymphatic System.—Dr. I. S. HODGSON-JONES.

T. R—, schoolboy, aged 16.

History.—Since birth swelling of the right side of the face, right leg and foot, and left arm has been present.

More recently he has had recurrent ascites, splenomegaly, hepatomegaly, and oedema of the lungs on several occasions.

The warty and pigmented lesions which may now be seen over his body appeared at the age of four years.

Family History.—Mother and two brothers are fit and well, but the father has kidney trouble. So far as is known, no member of the family has had anything resembling this condition; nor is there any known consanguinity between the parents.

Examination.—In addition to the swellings of the limbs and side of the face, numerous lesions resembling plane warts cover all four limbs, and on the chest and abdomen, pigmented macules are present in large numbers.

The ascites has been tapped a number of times. He developed intestinal obstruction, due to a fibrous adhesion in 1954, and at operation the spleen was found to have a number of currant-like nodules on its surface. There were also small cystic swellings on the transverse colon.

A McIndoe-Charles operation was done to relieve the oedema of the right leg. The lymphatic system was investigated by Professor J. B. Kinmonth with Patent Blue dye; dilation and stasis, with retention of the dye in the lymphatics for long periods was found.

Biopsy.—The histological picture of the skin lesions was found to be that of plane warts. Biopsy of subcutaneous tissue showed dilatation of lymphatic vessels and spaces.

Malignant change in the skin lesions is recorded in a significant number of cases of this sort in the literature. It appears as though an epithelioma may be developing on the dorsum of this child's foot.

Dr. R. G. HOWELL : Perhaps there may be some aetiological connexion between the lymphoedema and the warts. Most of the warty lesions seem to occur where the oedema is greatest, and the condition of his leg is not unlike the familiar post-inflammatory lymphoedemic leg with warty hyperkeratosis.

The PRESIDENT : How are you going to treat these warts?

Dr. HODGSON-JONES : I do not know how to deal with these; it is plainly going to be a very difficult task.

Dermatitis of the Scalp and Face Following the Use of Selsun.—Dr. L. FORMAN.

Mr. F. L—, aged 63 years.

This patient has had extensive psoriasis of the scalp and limbs for 33 years with a destructive arthritis of the hands and feet.

Three weeks ago his head was shampooed with Selsun because of "dandruff". The scaling may well have been due to dandruff. A further application of Selsun was made a week later. The next day the scalp was hot and swollen with swelling of the eyelids, and the face became involved within twenty-four hours. The skin showed the changes of an acute dermatitis, without exudation. There was also an itching erythema affecting the webs of the fingers.

I have seen one other case in which an acute dermatitis appeared on the scalp, spreading to the face, after the use of Selsun.

Ben. C. Eisenberg (1955, *Arch. Derm. Syph., Chicago*, **72**, 71) has reported three patients who developed recurrent attacks of dermatitis of the external auditory meatus and ear lobes, after using Selsun shampoo. Application of selenium sulphide suspension to the ears produced the dermatitis. The patients were able to continue with the use of the shampoo provided that the aural orifices and the ears were protected.

Dr. R. D. SWEET: I have not used Selsun much because when a traveller left a sample bottle I gave it to a member of the staff for his dandruff. He took three weeks to get better from the resulting dermatitis.

Dr. C. D. CALNAN: If you patch-test with Selsun and there is a positive reaction, it does not necessarily mean that it is allergic. We have seen many of these cases which are not acceptable as allergic sensitivity. Many of the cases described give no details of how the patch test was done; I am dubious if they are true allergic dermatitis.

Dr. BRIAN RUSSELL: When the traveller came to me I asked if he could also supply some of the vehicle as a control for clinical trials, believing that the vehicle might be as successful as Selsun itself. He did not do so and as a result I feel disinclined to give a trial to Selsun. To me, this case looks like a primary irritant type of dermatitis.

Dr. O. L. S. SCOTT: A white-haired, fussy patient of mine had been applying ung. emulsificans aquosum, B.P., for dandruff. She used Selsun without the preliminary shampoo. The ointment seemed to act like a mordant, for her hair remained yellow for at least 10 days afterwards.

Dr. N. A. THORNE: Manufacturers supplied me with a quantity of the Selsun shampoo base without the selenium sulphide and I found this very effective when used instead of the Selsun shampoo.

The following cases have been published in *Proc. R. Soc. Med.*, **49**, 423.

Dermatomyositis with Malignant Disease.—Dr. O. L. S. SCOTT.

Hydrargyria.—Dr. J. A. CARDNO and Dr. R. H. MEARA.

Primary Tuberculosis of the Skin.—Dr. R. H. MARTEN (for Dr. D. I. WILLIAMS).

Blue Naevus.—Dr. W. G. TILLMAN.

The following cases also were shown:

Premycotic Eruption.—Dr. P. F. BORRIE.

Orf (or ? Milker's Node).—Dr. BRIAN RUSSELL.

Necrobiosis Lipoidica.—Dr. LOUIS FORMAN.

A short paper on Methods of Measuring Blood Flow was read by Dr. H. E. HOLLING.

17 November 1955.

The following cases have been published in *Proc. R. Soc. Med.*, **49**, 231.

Acrodermatitis Enteropathica.—Dr. P. J. HARE and Dr. B. E. SCHLESINGER.

Pyoderma Gangrenosum.—Dr. STEPHEN GOLD.

Stomatitis for Diagnosis.—Dr. R. G. HOWELL (for Dr. G. B. MITCHELL-HEGGS).

Scleroderma.—Dr. M. FEIWEL and Dr. C. D. CALNAN.

The following cases also were shown.

Yaws.—Dr. DAVID ERSKINE.

Granuloma of the Foot for Diagnosis.—Dr. R. G. HOWELL (for Dr. G. B. MITCHELL-HEGGS).

Eczema of the Hands with Lymphoedema.—Dr. C. D. CALNAN (for Dr. G. B. DOWLING).

Sarcoidosis with Involvement of the Lips and Buccal Mucous Membrane.—Dr. ARTHUR ROOK and Dr. R. A. DAVIS.

Case for Diagnosis. ? Blue Naevus.—Dr. J. SAVAGE.

Dermatitis Nodularis Necrotica.—Dr. P. R. MONTGOMERIE (for Dr. E. J. MOYNAHAN).

Acquired Epidermolysis Bullosa.—Dr. P. F. BORRIE.

BOOK REVIEWS.

THE MEDICO-CHIRURGICAL ENCYCLOPAEDIA.*

THIS issue contains major articles by Touraine on Erythrodermia, Benign Tumours and Precancerous Dermatoses. They are dealt with lucidly and comprehensively though possibly an English writer would not include all the author's sub-groups, especially the infectious ones, among the erythrodermias. The same applies to the section on benign tumours in which we find among others silicotic granuloma, Weber-Christian disease and cheloid, and a purist might not place Paget's disease among the *precancerous* dermatoses. But apart from these minor criticisms the text is excellent and well illustrated with black and white pictures. Subsidiary articles deal with monilial infections following antibiotics, cutaneous torulosis, cutaneous myxoedema, lupus erythematosus and hydralazine, and other subjects culled rather spasmodically from the recent literature. The short but excellent account of cutaneous mastocytosis is particularly commended.

F. F. H.

THE FRENCH ATLAS.*

THE eleventh number contains an excellent description and illustration of the nodular elastosis described by Favre and Racouchot, a malady which does not seem to have reached many of the textbooks. There are also excellent pictures of anetodermia and Kyrle's Disease. This number includes also parapsoriasis en plaques, which is sharply distinguished from parapsoriasis en gouttes, in conformity with the view which has by now probably gained complete acceptance.

The twelfth number is mainly devoted to bullous eruptions. Under the name of Duhring-Brocq Disease are included a variety of eruptions which are distinguished by blisters and the absence of irritation, evolution in attacks and preservation of good general condition. This group is clearly very much larger than dermatitis herpetiformis, which is regarded as one particular type of the Duhring-Brocq group. Pemphigoid or bullous-pemphigoid is another member of this large group, and herpes gestationis is included here also. These authors adhere firmly to the view that acantholysis never occurs in these disorders and that it is characteristic of the true pemphigus group. The illustrations also serve to emphasize that the Duhring-Brocq diseases are by no means always herpetiform in appearance.

In the section on chronic benign familial pemphigus the distinction is well drawn between this disorder, bullous Darier's disease and the benign familial pemphigus of infants, described originally by Gougerot. The illustration of Hailey-Hailey disease is not very typical. There follows a complete section on the true pemphigus group, characterized by acanthosis. In view of the success of steroid treatment it is a little surprising that these authors give so much space to the use of arsenic, mercury and other older treatments.

The thirteenth section starts with scabies and in reading the text one becomes aware of the excellence of French descriptive dermatology, for the clinical manifesta-

* *Recueil Périodique de l'Encyclopédie Médico-Chirurgicale*. No. 30, Cahier spécialisé de Dermatologie. (1956). Ed. A. Touraine. Paris: Editions Technique.

* *Atlas de Dermatologie*. By P. de Graciansky and S. Bouille, Paris: Librairie Maloine S. A. To be issued in 20 parts, price 2000 Francs each. London: H. K. Lewis. Prospectus on request.

tions of that disease have been dealt with extremely well. There follows a section on keratoacanthoma in which it is pleasant to see that British authors receive full credit. There is a good section on porphyria which contains a review of recent literature and a most adequate summary of this group of disorders.

A considerable section deals with the pathology and serology of syphilis occupying 27 pages and including a valuable appraisal of serum reactions and the treponema immobilization test of Nelson. Illustrations continue their usual standard; pediculi, particularly, shining golden against a pale purplish background, their nits hanging like dewdrops from hairs, seem more in the tradition of oriental watercolour than medical illustration.

F. R. B.

VENEREAL DISEASE LEGISLATION.*

This little publication lists the state of the law in various countries in regard to the notification of venereal disease, contact tracing, compulsory examinations and treatment. It mentions also laws in respect of the duties of medical practitioners, restriction of employment for infected people and the organization of venereal disease control. In this short compass, of course, little detail can be given and no mention is made of the extent to which various countries enforce their laws or with what results.

It is interesting to observe that England and Wales have about the least legislation in this regard and apparently also the most antiquated.

F.R.B.

CORRESPONDENCE.

The Editor, 'The British Journal of Dermatology.'

SIR,—I have recently had the privilege of visiting some of the leading dermatological centres in North America and this has given me the opportunity of contrasting their postgraduate training with our own. Broadly speaking the difference is that between an apprentice system in England and a didactic one in the United States, with Canada somewhere in between. The apprentice system has many advantages, especially when the master is an outstanding man; but often too much of the apprentice's time is taken up with carrying tools and making cups of tea, or in dermatological language—seeing vast numbers of old patients without adequate supervision.

In the old days of medical apprenticeship, the student lacked training in the basic sciences and the same applies to our dermatological apprentices to-day. How many of our registrars have had any real basic training in radiotherapy or mycology—to say nothing of the bacteriology or chemical pathology of the skin? It is sometimes maintained that the good man will seek out such training for himself and that there is no need to spoon-feed him by set courses or prescribed periods of laboratory work, such as the American Board requires.

I do not accept this for two reasons. First, the registrar is too involved under the N.H.S. in routine work, and second, our dermatological centres do not provide the opportunity for training in the relevant basic sciences. Here and there certain courses may be available but I do not believe any school in the country covers all.

* *Venereal Diseases: A Survey of Existing Legislation.* (1956). Geneva: World Health Organisation. Pp. 44.

I am convinced from my visit to America that we are lagging behind in our post-graduate training of dermatologists and that before long this will reflect on the whole standard of British dermatology. To remedy this I appeal to the British Association of Dermatology to set up a committee to enquire into the whole subject of post-graduate training as an urgent matter.

Yours faithfully,
F. F. HELLIER.

Leeds,
6 July 1956.

The Editor, 'The British Journal of Dermatology'

SIR,—The acanthomata which Dr. Murray G. Williams has observed appearing after eczema (p. 268) would be most easily explained as small seborrhoeic warts, which I am sure that they are. The points which trouble him in making this diagnosis are the small size of the lesions, their paleness, their absence of scaling, their ability to disappear, their occurrence on the limbs, their development in association with eczema, and finally their histopathology.

Not one of these distinctions is valid. If one examines a skin which is liberally endowed with seborrhoeic warts one can see them in all sizes from pin-head to 3 cm. across, the larger the wart the darker and more scaly, and *vice versa*. Although seborrhoeic warts are often permanent they can disappear spontaneously just as common warts do, and like them can multiply exceedingly on an eczematous skin. Seborrhoeic warts are by no means confined to the so-called seborrhoeic areas, though they reach their greatest development in them; they can on occasion be found almost anywhere except on the palms and soles. The simple histopathology which Dr. Williams records in his acanthomata offers no difficulty when one considers the histopathology of the plane as compared with the common wart.

If Dr. Williams can accept my statements he should be impressed with the great weight of evidence which he has recorded in favour of his acanthomata being the young of seborrhoeic warts. The common site of the lesions was the back and front of the chest, the patients were in the older age group, and three out of four had in addition numerous seborrhoeic keratoses. More often the lesions were situated among already existing seborrhoeic keratoses. After a period most of the lesions had disappeared but a few became slightly darker in colour and were then indistinguishable from seborrhoeic keratoses. The clinical photograph shows lesions of differing size but similar morphology.

I hope that he can agree with me on this matter and then we are both faced with a single problem—the cause of seborrhoeic warts: On which topic we are already one in believing the constitutional background to be of the greatest importance.

I am, Sir,
Yours, etc.,
ALAN LYELL.

Aberdeen,
August, 1956.

CURRENT LITERATURE

EXPERIMENTAL INVESTIGATIONS ON MECHANISM PRODUCING ACUTE DERMATOPHYTOSIS OF FEET. R. L. BAER, S. A. ROSENTHAL, J. Z. LITT and H. ROGACHEFSKY. (1956) *J. Amer. med. Ass.*, **160**, 184.

Sixty-eight volunteers (clinically and mycologically non-infected) immersed their feet for 30 minutes in foot-bath water heavily contaminated with dermatophytes. No case of clinical fungus disease resulted, although mycelium was found on one or both feet of 54% during the 6 weeks after exposure. Four of twenty fungus-infected volunteers, who immersed their feet in water contaminated with a different species, developed a superinfection. The authors conclude that the feet of persons with clinical fungous disease may be inherently more susceptible than those free from clinical infection to the temporary establishment of another species of dermatophyte.

Since exogenous exposure plays, at most, a minor role in causing active attacks of fungous disease of the feet public health services should be based on the maintenance and increase of local resistance to infection rather than on largely useless measures designed to prevent infection.

A. J. R.

FURTHER STUDIES ON MELANOCYTES AND MELANOGENESIS IN THE HUMAN FOETUS AND NEWBORN. S. W. BECKER and A. A. ZIMMERMAN. (1955) *J. invest. Derm.*, **25**, 103.

While it is generally accepted for amphibia that the original melanoblasts in the skin have migrated from the neural ridge, though they may afterwards multiply locally, it has never been possible to prove the same origin in mankind; and rival theories continue to flourish. Indeed the only evidence of this origin is that the foetal distribution of melanoblasts tends to reflect the pattern of development of the neural canal. One of the difficulties is the lack of a stain capable of distinguishing melanocytes from the nonspecific connective tissue elements from which they are supposed to become morphologically indistinguishable during their passage through the corium.

The authors have extended earlier studies of staining methods and have accumulated further details of the development of the cutaneous pigmentary system.

J. H. T. D.

PROTEINS OF MAMMALIAN EPIDERMIS. C. CARRUTHERS, D. L. WOERNLEY, A. BAUMLER and B. KRESS. (1955) *J. invest. Derm.*, **25**, 89.

This account, of electrophoretic studies of protein extracted from epidermis with solutions of urea and of sodium lauryl sulphate, underlines the complexity of the subject—by demonstrating, for example, the powerful effect of minor details of extraction procedure on the product.

The tissues used were derived from the snouts of cattle, for the sake of its thickness; from human epidermis, for its strong differentiation; and from that of mice for its lack of it. Differentiation in the epidermal cell is a function of the polymerization of its protein molecules. The correspondence of chemical properties with x-ray diffraction findings and the characters of the linkages at various stages between the corpuscular particles of the basal layer, the tonofibrils higher up, and the end-product in the various forms of hardened keratin, are discussed.

J. H. T. D.

NUTRITIONAL REQUIREMENTS OF DERMATOPHYTES IN CONTINUOUS SHAKE CULTURE.

F. RAUBITSCHKE. (1955) *J. invest. Derm.*, **25**, 83.

When the broth in which fungus is growing is kept in constant agitation at 30–32° C. there are formed pellets, regular and constant in size for each organism, each consisting of a tangled mass of mycelium having arthrospores and chlamydospores but without the reproductive organs ordinarily seen in culture—thus closer to the forms assumed in parasitic conditions. In these conditions all except *E. floccosum* managed with the sole addition to the saline of ammonium sulphate, having presumably obtained their carbon from the atmosphere.

J. H. T. D.

FLUORINATED HYDROCARBON COMPOUNDS ("FREON") AS A REFRIGERANT IN SURGICAL SKIN PLANING. A. S. STERNBERG. (1955) *J. invest. Derm.*, **25**, 77.

Recommends a mixture of the fluorinated hydrocarbons known as "Freon 12" and "Freon 114". Method of using it is not described; and while boiling points and freezing points are given, there is no information about such properties as critical temperature or latent heat of evaporation.

J. H. T. D.